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INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 5 : A61K 31/50

A1

(11) International Publication Number: WO 93/21921

(43) International Publication Date: 11 November 1993 (11.11.93)

(21) International Application Number: PCT/FI93/00191

(22) International Filing Date: 5 May 1993 (05.05.93)

(30) Priority data:
9209769.0 6 May 1992 (06.05.92) GB

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(81) Designated States: AU, BG, BR, CA, CZ, FI, HU, JP, KP, KR, NO, NZ, RO, RU, SK, UA, US, European patent (AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE).

Published
With international search report.

(54) Title: ANTI-ISCHEMIC MEDICAMENT

(57) Abstract

[[4-(1,4,5,6-tetrahydro-4-methyl-6-oxo-3-pyridazinyl)phenyl]hydrazono]propanedinitrile which has been previously suggested for the treatment of congestive heart failure is useful in the treatment of myocardial ischemia.

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ANTI-ISCHEMIC MEDICAMENT

The present invention relates to the use of [[4-(1,4,5,6-tetrahydro-4-methyl-6-oxo-3-pyridazinyl)phenyl]hydrazono]propanedinitrile (I) or its enantiomers or pharmaceutically acceptable salts thereof in the manufacture of a medicament for the treatment or prevention of myocardial ischemia.

[[4-(1,4,5,6-tetrahydro-4-methyl-6-oxo-3-pyridazinyl)phenyl]hydrazono]-propanedinitrile (I) has been earlier described in European patent application EP 383449. It has been shown that compound (I) may be potent in the treatment of congestive heart failure. The optically pure enantiomers of this compound has previously been described in the patent application PCT/FI92/00003. It has now been revealed that compound (I) and its optically active enantiomers also have significant anti-ischemic properties.

The method for the preparation of compound (I) and the resolution of its optically active (-) and (+) enantiomers are described in the patent applications mentioned above. Salts of these compounds may be prepared by known methods. Pharmaceutically acceptable salts are useful as active medicaments, however, preferred salts are the salts with alkali or alkaline earth metals.

In EP 383449 it was shown that compound (I) has significant calcium dependent binding to troponin and is a potent inhibitor of PDE III enzyme. Like other PDE III inhibitors, such as pimobendan and milrinone, compound (I) increases contractility of the cardiac muscle and produces vasodilatation and has therefore utility in the treatment of congestive heart failure. The anti-ischemic utility of positive inotropic compound (I) which is a potent PDE III inhibitor was unexpected because arrhythmic effects have often been observed in connection with PDE III inhibitors. We have found that, unlike pimobendan or milrinone, compound (I) can decrease calcium influx. This may play some role in the observed new effect of compound (I) and its enantiomers.

The anti-ischemic compound according to the invention is formulated into dosage forms using the principles known in the art. It is given to mammalian organisms, i.e., humans, a patient as such or in combination with suitable pharmaceutical excipients in the form of tablets, dragees, capsules,

suppositories, emulsions, suspensions or solutions whereby the contents of the active compound is in the formulation from about 0.5 to 100 % per weight. In general, the compound of the invention may be administered to man in oral doses ranging from about 1 to 100 mg per day once a day or divided into several doses. Choosing suitable ingredients for the composition is a routine for those of ordinary skill in the art. It is evident that suitable carriers, solvents, gel forming ingredients, dispersion forming ingredients, antioxidants, colours, sweeteners, wetting compounds and other ingredients normally used in this field of technology may be also used. The compositions of the present invention have anti-ischemic activity and are of use in the treatment and prevention of myocardial ischemia. Such conditions can be treated by administration of the compounds according to the invention for example orally, rectally or parenterally.

The anti-ischemic properties of the compounds according to the invention are demonstrated below.

The effects of [[4-(1,4,5,6-tetrahydro-4-methyl-6-oxo-3-pyridazinyl)-phenyl]hydrazono]propanedinitrile on ventricular arrhytmias, survival rate and infarct size after coronary artery ligation were studied in conscious rats (male Sprague-Dawley rats). Anesthetized rats were opened at the fourth intercostal space and a silk loop was placed around the left main coronary artery, about 3 mm from its origin. After complete recovery (7-10 days) from this preliminary surgery, the coronary ligature was tightened in the conscious rats to produce acute coronary artery occlusion. [[4-(1,4,5,6-tetrahydro-4-methyl-6-oxo-3-pyridazinyl)phenyl]hydrazono]propanedinitrile in doses of 0.06 and 0.20 mg/kg (in NaCl solution) was given intravenously 5 min prior to the ligation. A bipolar ECG was recorded continuously. The survival rate and the incidence of arrhytmias were registered in accordance with the Lambeth Conventions. In the animals that survived for 16 hours, the size of the infarcted area was measured after staining with nitroblue-tetrazolium dye.

The results (Table 1) show that [[4-(1,4,5,6-tetrahydro-4-methyl-6-oxo-3-pyridazinyl)phenyl]hydrazono]propanedinitrile increased the survival rate and decreased the incidence of arrhytmias as compared with the control group. In addition the incidence of ventricular tachycardia decreased from 82 % in the controls to 53 % after the lower and to 28% ($p<0.01$) after the higher dose (this data not shown in Table 1). Figure 1 shows that [[4-(1,4,5,6-tetrahydro-4-methyl-6-oxo-3-pyridazinyl)phenyl]hydrazono]propanedinitrile also decreased the infarct size dose-dependently.

TABLE 1.

Acute phase			
Dose (mg/kg)	n	Survival (%)	No arrhythmia (%)
Control	17	65	18
0.06	15	93*	33
0.20	14	100**	64**

* $p<0.05$, ** $p<0.01$

The effects of optically pure enantiomers of [[4-(1,4,5,6-tetrahydro-4-methyl-6-oxo-3-pyridazinyl)phenyl]hydrazono]propanedinitrile were also studied. The experiment was performed as above with the exception that the ligation was placed around the left coronary artery about 2 mm from its origin. The doses were 0.06 and 0.20 mg/kg (in Na_2HPO_4 solution) for both (-) and (+) enantiomer of [[4-(1,4,5,6-tetrahydro-4-methyl-6-oxo-3-pyridazinyl)phenyl]-hydrazono]propanedinitrile. The results for the (-)-enantiomer are shown in Table 2 and for the (+)-enantiomer in Table 3. Both enantiomers increased the number of animals which did not develop any arrhythmias. In addition, the (+)-enantiomer showed survival rate increasing effect.

TABLE 2.

Acute phase			
Dose (mg/kg)	n	Survival (%)	No arrhythmia (%)
Control	17	76	0
0.06	11	64	18*
0.20	17	65	35**

* $p<0.05$, ** $p<0.01$

TABLE 3.

Acute phase			
Dose (mg/kg)	n	Survival (%)	No arrhythmia (%)
Control	20	40	5
0.06	14	57	21
0.20	13	69*	15

* $p<0.05$, ** $p<0.01$

The results indicate that [[4-(1,4,5,6-tetrahydro-4-methyl-6-oxo-3-pyridazinyl)phenyl]hydrazono]propanedinitrile and its enantiomers afford significant protection against ischemia-induced arrhythmias and the development of irreversible myocardial damage. These compounds have therefore utility as anti-ischemic agents in the treatment or prevention of myocardial ischemia.

Claims

1. Use of [[4-(1,4,5,6-tetrahydro-4-methyl-6-oxo-3-pyridazinyl)phenyl]-hydrazono]propanedinitrile or a pharmaceutically acceptable salt thereof in the manufacture of a medicament for the treatment or prevention of myocardial ischemia.

2. Use according to claim 1 wherein [[4-(1,4,5,6-tetrahydro-4-methyl-6-oxo-3-pyridazinyl)phenyl]hydrazono]propanedinitrile is substantially free of the (+)-enantiomer.

3. Use according to claim 1 wherein [[4-(1,4,5,6-tetrahydro-4-methyl-6-oxo-3-pyridazinyl)phenyl]hydrazono]propanedinitrile is substantially free of the (-)-enantiomer.

4. A method for treating myocardial ischemia in a mammalian organism, said method comprising administering an effective amount to treat myocardial ischemia of [[4-(1,4,5,6-tetrahydro-4-methyl-6-oxo-3-pyridazinyl)phenyl]-hydrazono]propanedinitrile or its enantiomer or a pharmaceutically acceptable salt thereof.

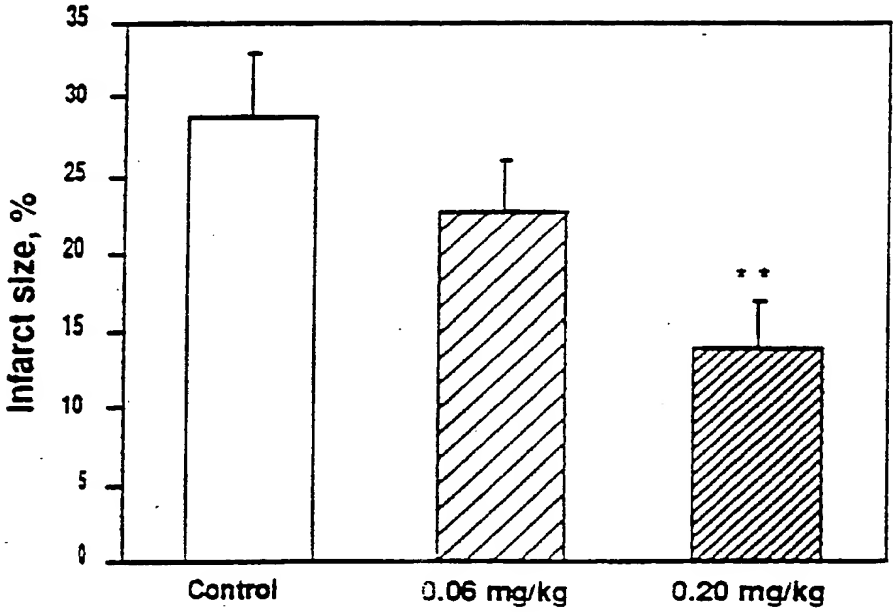

FIG. 1

INTERNATIONAL SEARCH REPORT

International Application No PCT/FI 93/00191

I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate all)[6]

According to International Patent Classification (IPC) or to both National Classification and IPC

Int.Cl. 5 A61K31/50

II. FIELDS SEARCHED

Minimum Documentation Searched[7]

Classification System	Classification Symbols
Int.Cl. 5	A61K

Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in the Fields Searched[8]

III. DOCUMENTS CONSIDERED TO BE RELEVANT[9]

Category °	Citation of Document,[11] with indication, where appropriate, of the relevant passages[12]	Relevant to Claim No.[13]
P,A	WO,A,9 212 135 (ORION-YHTYMÄ OY) 23 July 1992 cited in the application see the whole document	1-4
A	EP,A,0 383 449 (ORION-YHTYMÄ OY) 22 August 1990 cited in the application see the whole document	1-4
A	EP,A,0 233 745 (SMITH KLINE & FRENCH LABORATORIES LTD.) 26 August 1987 see abstract	1-4
A	US,A,4 962 110 (J.C. EMMETT) 9 October 1990 see claims 1,13-21	1-4

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IV. CERTIFICATION

Date of the Actual Completion of the International Search	Date of Mailing of this International Search Report
30 JUNE 1993	26. 07. 93
International Searching Authority	**Signature of Authorized Officer**
EUROPEAN PATENT OFFICE	FOERSTER W.K.

Form PCT/ISA/210 (second sheet) (January 1985)

ANNEX TO THE INTERNATIONAL SEARCH REPORT ON INTERNATIONAL PATENT APPLICATION NO.

FI 9300191
SA 73901

This annex lists the patent family members relating to the patent documents cited in the above-mentioned international search report. The members are as contained in the European Patent Office EDP file on 30/06/93
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For more details about this annex : see Official Journal of the European Patent ffice, No. 12/82

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INTERNATIONAL APPLICATION PUBLISHED UNDE WO 9321921A1

(51) International Patent Classification 5 :		(11) International Publication Number: WO 93/21921
A61K 31/50	A1	(43) International Publication Date: 11 November 1993 (11.11.93)

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* (Referred to in PCT Gazette No. 10/1996, Section II)

BNSDOCID: <WO___9321921A1_IA>

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